PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Attorney Docket No.: 9896.129.3.1.1

CHUDZIK, et al.

Application No.: 09/989,033 Examiner: Chen, B.

Filed: November 21, 2001 Group Art Unit: 1762

For: BIOACTIVE AGENT RELEASE COATING

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**AFFIDAVIT UNDER 37 CFR 1.132**

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

State of Minnesota )
) S.S.
County of Hennepin )

Dr. Aron B. Anderson, Ph.D., being first duly sworn, deposes and says:

1. I am Aron B. Anderson. I am currently employed at SurModics, where I have worked for 13 years. During my employment at SurModics, I have worked for about 10 years on development, testing, and commercialization of drug delivery coatings and matrices. I have also worked for about 10 years on development, testing, and commercialization of coatings to improve the blood compatibility of medical device materials. I received a Ph.D. degree in Chemical Engineering from Stanford University in 1991. I received a B.S. degree in Chemical Engineering from the University of Minnesota in 1985.

2. This affidavit is being submitted to provide an explanation of polyalkyl(meth)acrylates (PAMA) and their crosslinkability characteristics.

3. Acrylate or methacrylate polymers are composed of monomers as shown in Figure 1. In acrylate polymers, the $R_2$ group is a hydrogen atom (-H); in methacrylate polymers, the $R_2$ group is a methyl group ($-CH_3$). Alkanes are hydrocarbon molecules composed of only hydrogen and carbon atoms, containing only single bonds between adjacent carbon atoms and between the carbon and hydrogen atoms. Alkyl groups are alkane-based substituents which exist as a subunit of a larger organic molecule. As an example, butane ($CH_3$-$CH_2$-$CH_2$-$CH_3$) is an alkane and the butyl group has the same structure as butane minus a hydrogen atom (-H). The location of the subtracted hydrogen atom is where the alkyl group may be bonded to other chemical structures. Alkyl acrylates or alkyl methacrylates, therefore by definition, have alkyl groups as the $R_1$ group in Figure 1.

4. One feature of alkyl groups is that they are relatively stable molecules, which have no particular reactivity toward each other or toward other organic molecules. One of the few reactions possible with alkanes is combustion with oxygen to form water and carbon dioxide, whereby the alkane structure is completely degraded. This process only occurs at high temperatures, beyond where polymers are typically processed. Because of this lack of reactivity among alkanes, there is no specific mechanism whereby an alkane or an alkyl side group on a polymer will react with other alkyl side groups on the same or an adjacent polymer. For this reason alkyl methacrylate polymers are not considered to be crosslinkable under typical polymer processing conditions.

5. Monomers used in methacrylate or acrylate polymers can be combined with other monomers to form the backbone of a single polymer (now referred to as a co-polymer). If the other monomer or monomers contain reactive side groups as part of their structure, it would then be possible to have sites for crosslinking along the chain of the resulting co-polymer. It should be noted, however, that if other reactive side group monomers are included in the polymer structure, then the polymer is no longer a "polyalkyl(meth)acrylate" or a "polyalkyl acrylate." Typical reactive groups used for crosslinking of polymers include chemistries such as: thiols, carbon-carbon double bonds, carbon-carbon triple bonds, amines, hydroxyls, epoxides, and aldehydes.

6. Poly(butyl methacrylate) (PBMA) is a particular example of an alkyl methacrylate polymer. Referring to Figure 1, $R_1$ is a butyl group and $R_2$ is a methyl group in the PBMA polymer. As discussed above for polyalkyl(meth)acrylates in general, this particular polymer does not have reactive groups to form crosslinks. The butyl group, the methyl group and the hydrogen atoms on the carbon-carbon backbone do not have the proper reactivity to form crosslinks within the polymer or between adjacent polymers.

7. The polymer polyethylene vinyl acetate (PEVA; Figure 2) also does not have groups present in its structure that allow crosslinking of the polymer. The hydrogen atoms on the backbone and the methyl group on the end of the acetate sidechain do not have sufficient reactivity to allow crosslinking reactions to occur. As with the alkyl methacrylates discussed above, other monomers could be included along with the ethylene and the vinyl acetate to provide the capability to crosslink the polymer to itself or to adjacent polymers, but then the polymer would no longer be "polyethylene vinyl acetate".

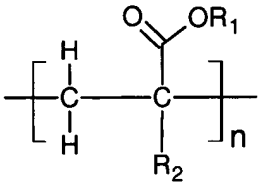


Figure 1 - PAMA

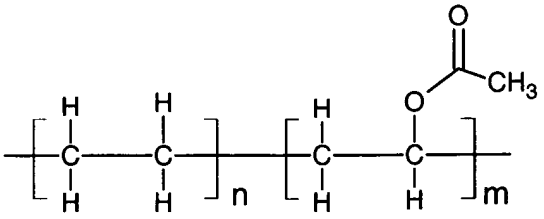


Figure 2 – PEVA

Dr. Aron B. Anderson, Ph.D. 12-8-2004

Subscribed and sworn to before me
this 8th day of DECEMBER, 2004.

Notary Public

#3051418\1

KATHLEEN G. WISE
NOTARY PUBLIC - MINNESOTA
My Commission Expires Jan. 31, 2005

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2. This affidavit is being submitted to clarify the advantages of the combination of the hydrophobic polymer blend of polyalkyl(meth)acrylate (PAMA) and poly(ethylene-co-vinyl acetate) (PEVA) over a single polymer matrix material.

3. In designing a drug delivery matrix, it is beneficial to have flexibility in the control of the release rate of a drug for any particular loading or dose of the active compound. A single polymer component used for a delivery matrix is generally limited to a narrow range of release rates defined by the intrinsic physical and chemical properties of the polymer. As a particular example of this limitation, we determined that the release rates of several drugs from a PEVA polymer matrix were faster than desired. In addition, the degree to which the release rate could be varied with a PEVA polymer was quite narrow, especially for a given dose of the drug. Alternately we discovered that the release rate of these same drugs from a PAMA, such as polybutyl methacrylate (PBMA), polymer matrix were slower than desired. The variation in rate achievable with PAMA alone was also narrow.

4. In addition to the limitations on the drug release properties, we discovered that individually these two polymer matrix materials had insufficiencies in their physical properties. In general, we found that drug/PEVA matrices were too soft and, thus, not durable enough for certain applications, including stent coatings. Drug/PEVA coatings were more easily deformed or damaged by shear or normal forces. Conversely, the drug/PAMA matrices were too stiff and brittle for certain applications, including stent coatings. Although they were more durable to normal forces, drug/PAMA matrices showed cracks under deformation and extension forces.

5. Unexpectedly, it was discovered that blends of these two polymers improved both the physical and drug release properties. Blended matrices were more flexible to deformation. Coatings made with the blended polymers did not easily crack or tear. The PEVA/PAMA/drug matrices were more durable and tolerated shear and extension forces much better than the individual components. The blend matrices allowed optimal drug release properties to be achieved. In addition the drug release rate could be modulated both faster and slower, over a wide range of rates, simply by changing the ratio of the two polymers in the matrix, even while

keeping the dose (loading) of drug constant in the matrix.

Dr. Aron B. Anderson, PhD. 12-8-2004

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2. This affidavit is being submitted to explain the advantages of hydrophobic polymeric coatings including bioactive agents versus hydrophilic polymeric coatings including bioactive agents.

3. In preparing a coating matrix to control the release of a drug, it is advantageous in some applications for the coating matrix to limit the uptake of water. Coatings which swell significantly in water will yield faster release rates, as the water enters the matrix and provides the driving force and the pathway for the drug to leave the matrix and reach the surrounding medium. Hydrophilic polymers are designed to swell significantly in water. If a drug is contained in a hydrophilic polymer, and this hydrophilic polymer matrix is placed in an aqueous environment, the matrix will swell with water and the drug will either be expelled from the matrix by the invading water or the water will provide a channel for the drug to diffuse out of the matrix into the surrounding medium. Thus, such hydrophilic polymer matrices do not provide a significant amount of control of drug release compared to a coating matrix which primarily excludes water.

4. The hydrophobic polymer combination blend of one or more polyalkyl(meth)acrylates (e.g. polybutylmethacrylate) and poly(ethylene-co-vinyl acetate), limit the uptake of water when placed in an aqueous environment; e.g. less than about 1-2% by weight. Thus, a drug blended into a matrix containing these polymers will be required to diffuse through the polymer structure rather than follow the interconnected water phase to reach the surrounding medium. Because of the low water content found in and allowed to enter hydrophobic polymers it is possible to have more control over the drug release.

5. Coatings which swell in water will also not have as much durability as coatings that minimize water uptake. The water present in the matrix will serve as a plasticizer, softening the polymer and making it more susceptible to shear, normal, or extension forces. The more water taken up by the polymer or polymer blend, the less durable the matrix will be. Conversely, a coating formed of a hydrophobic polymer blend of one or more polyalkyl(meth)acrylates and poly(ethylene-co-vinyl acetate) will swell insignificantly in water and thus will maintain the

same physical properties it had prior to placement in an aqueous environment, while also providing other advantages over hydrophilic polymers.

Dr. Aron B. Anderson, PhD. 12-8-2004

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